Oncology and Translational Medicine
DOI 10.1007/s10330-019-0362-2

October 2019, Vol. 5, No. 5, P229–P236

ORIGINAL ARTICLE

Treatment results of childhood extracranial malignant germ cell tumors and the salvage approach for recurrent and refractory cases: a single-center report

Kejun He, Xiaojun Yuan (✉), Zhen Tan

Department of Pediatric Hematology/Oncology, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200092, China

Abstract

Objective The aim of this study is to report the treatment result of childhood excranial malignant germ cell tumors and discuss the experience for recurrent and refractory cases treatment from our center.

Methods We have retrospectively analyzed 58 extracranial malignant germ cell tumor patients treated with surgery and chemotherapy from our center over a 9-year period. Another 14 recurrent and refractory cases referred from other centers were added to the study for salvage approach. We evaluated the treatment results for primary cases and relapsed cases with a median follow-up of 61.5 months. Several factors were analysed to evaluate their power to the outcome of these cases.

Results The 5-year event-free and overall survival for primary cases were 74.1±5.7% and 86.2±4.5%, respectively. 25 recurrent or refractory cases entered the salvage approach study, and 17 patients were alive till the end of follow-up. We demonstrated superior survival outcome for those with successful local control through pre-operative and post-operative radiotherapy, second-look surgery and multi-drug second-line chemotherapies.

Conclusion The outcome for childhood extracranial malignant germ cell tumors is generally favorable. For recurrent and refractory cases, multi-modality treatment approaches including radiotherapy, salvage chemotherapy and secondlook surgery are important for better local control.

Received: 29 May 2019
Revised: 10 June 2019
Accepted: 25 June 2019

Key words: chemotherapy; germ cell tumor; radiotherapy; surgery; children

Germ cell tumors (GCTs) are infrequent in childhood, developing at a rate of 2.4 cases per million children and representing approximately 2% to 3% of cancers diagnosed in children and adolescents aged < 15 years [1]. Extracranial GCTs can be categorized as gonadal or extragonadal according to their original sites. GCTs are derived from pluripotent precursor cells known as primordial germ cells, yet they can present as a heterogeneous group of tumors in distinct phenotype [2]. Yolk sac tumors (YSTs), the most common pure malignant GCTs in young children, are confirmed if the precursor cells differentiate to resemble extraembryonic structures. Malignant teratomas (MTs) are teratomas containing at least one of the malignant germ cell elements. YSTs and MTs account for most of the extracranial malignant germ cell tumors (MGCTs) in children and young adolescents [3].

The treatment outcome for childhood MGCTs has greatly improved in the past two decades due to the introduction of platinum-based chemotherapy along with effective pediatric surgery and better supportive care [4–6]. Despite these achievements, approximately 15% of the cases are recurrent or refractory. These cases would have dismal prognosis if no effective salvage treatment was performed, especially in patients from developing countries with limited medical resources [4, 7]. This report has two aims: (1) to study the result of current treatment with surgery and carboplatin, etoposide, bleomycin (JEB) regimen chemotherapy for extracranial MGCTs in

✉ Correspondence to: Xiaojun Yuan. Email: xhxjyuan@hotmail.com

Chinese children and (2) to evaluate the safety and efficacy of the multimodality salvage approach for recurrent and refractory MGCT cases in our center.

Patients and methods

Patients diagnosed with MGCTs between March 2007 and December 2015 at Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine were enrolled. The recurrent or refractory cases along with cases referred from other centers during this period were analyzed in the study on the salvage approach. Recurrent cases were defined as cases that relapsed after remission, and refractory cases as no or minor response to conventional treatment. Clinical and laboratory data were collected from patients' medical records.

The diagnosis of MGCT was confirmed through histopathologic examination of surgical resection or biopsy specimen and serum tumor marker [α-fetoprotein (AFP) and β-human chorionic gonadotropin] test by experienced pathologists. Since AFP levels have a wide variation and variability in $t_{1/2}$ at different ages within the first year of life, we obtained established normal ranges at various ages as reference for evaluation [8]. The Children's Oncology Group (COG) criteria of gonadal and extragonadal tumors were used for staging [9]. Imaging evaluation for staging included computed tomography of the chest, brain, and original site and technetium-99m bone scan.

In our center, a multidisciplinary consultation of any patient suspected of having GCT was organized to discuss the probable histology and optimal surgical approach. Radical surgery would be performed if this was possible without major morbidity. Delayed resection following biopsy and neoadjuvant chemotherapy was implemented to prevent mutilating surgery and ensure complete resection afterward. When a high-risk procedure is encountered at presentation or malignant histologies are strongly suspected (elevated markers), biopsy could be omitted in the premise that surgery was planned in the short term. Radical inguinal orchiectomy was performed on the testicular tumor with high ligation of the spermatic cord. Coccygectomy was performed with excision of the original tumor in sacrococcygeal cases.

JEB regimen was used for chemotherapy in our center. Stage I testicular tumors were monitored after radical resection if the marker was negative. Otherwise, chemotherapy was performed. Chemotherapy was performed in patients with infantile immature teratoma who developed malignant YST recurrence. These children were categorized into the malignant teratoma group in the analysis. The JEB regimen consists of etoposide (120 mg/m^2 infusion on days 1–3), carboplatin (600 mg/m^2 infusion on day 2), and bleomycin (15 mg/m^2 infusion on day 3). If the glomerular filtration rate (GFR) could be obtained, the formula for carboplatin dosage was used [10]:

$$D\ (mg/m^2) = \text{target } AUC\ (mg \cdot min/mL) \times [0.93 \times GFR\ (mL/min/m^2) + 15]$$

The target area under the plasma carboplatin concentration-vs-time curve (targetAUC) was set as 6 mg•min/mL in the JEB regimen for MGCTs. Radiotherapy (RT) and second-look surgery were the major approaches for patients with recurrent and refractory tumors. Local irradiation with a total volume of 27.0–50.4 Gy was performed by the RT team of our center. Second-look surgery was performed to re-excise the lesion and sampling for histologic re-evaluation. We assessed and categorized tumor response after surgery as follows: R0, tumor totally removed, no residual tumor detectable macroscopically or microscopically; R1, tumor mostly removed, no tumor detectable macroscopically but residual tumor tissue detected microscopically; and R2, tumor resection, residual tumor detectable macroscopically.

Second-line chemotherapy regimens including PEI (cisplatin 20 mg/m^2 infusion on d1–5, etoposide 100 mg/m^2 infusion on days 1 to 5, and ifosfamide 1.5 g/m^2 infusion on d1–5) [11] and IN (irinotecan 10 mg/m^2/dose 5 days a week for 2 weeks and nedaplatin 100 mg/m^2 on d1) [12–13] were preferred in cases with poor response to JEB regimen. Courses were conducted every 21–28 days depending on hematologic recovery. Chemotherapy response was indicated by a decrease in tumor in size in imaging or a satisfactory calculated decline in tumor marker. It was considered that remission was achieved when AFP levels had normalized, in which time imaging showed generally either confirmed remission or considerable reduction in tumor size. Two further courses were conducted after

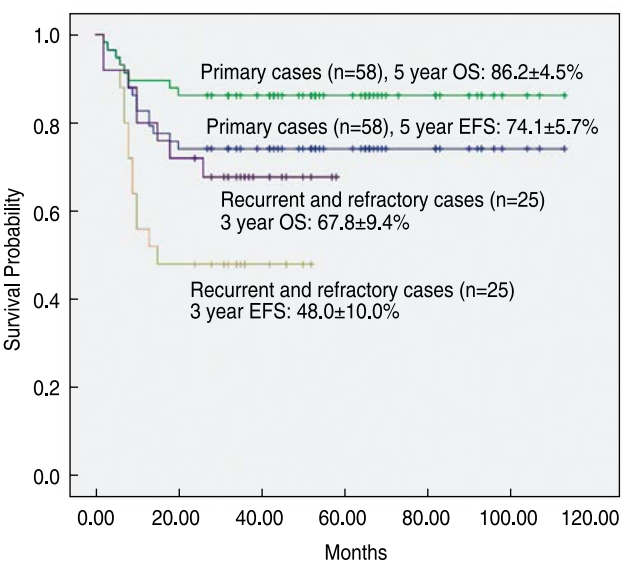

Fig. 1 Survival curve of two patient groups for EFS and OS

complete remission for consolidation. Patients with recurrent and refractory tumors were treated under the supervision of a multidisciplinary team of our center, and this treatment protocol for MGCTs was approved by the hospital's ethics committee. The general treatment plan for MGCTs was shown in Fig. 1.

The last follow-up date was December 31, 2017. Overall survival (OS) or event-free survival (EFS) was calculated as time (in months) from diagnosis to death of any cause or event. Event included disease progression, recurrence, or abandonment.

The tumor marker was examined monthly after treatment completion in the first year of follow-up, then every three months in the second and third years, and every six months in the fourth and fifth years. Physical examination and necessary imaging evaluation were also performed every visit.

The NCI Common Terminology Criteria for Adverse Events (CTCAE, version 4.03) was used in the toxicity assessment.

Data analysis was performed using Statistical Package for the Social Sciences version 20.0 (IBM, USA). The survival rates were reported as mean ± standard SE using the Kaplan-Meier method. Comparison of survival between the different groups was performed using the bilateral log-rank test. A P-value < 0.05 was considered statistically significant. A multivariate analysis using a proportional hazards model was conducted to identify risk factors and the risk model.

Results

In a 9-year period, 72 patients with MGCT were enrolled, with a median follow-up duration of 61.5 months (2–113 months). There were 30 boys and 42 girls.

Among 58 primary cases that were initially diagnosed and treated in our center, the subtypes included YST (46), malignant teratoma (11), and dysgerminoma (one ovarian case). The age of the patients ranged from 6 months to 12 years (due to the age limitation for admission) with a median of 26.5 months. According to the COG staging system, the numbers of cases classified as stages I, II, III, and IV were 12, 6, 24, and 16, respectively. The primary sites and their histologic diagnosis are summarized in Table 1. Four patients with stage I testicular YST underwent chemotherapy according to the guardians' strong willingness and physicians' approval and have EFS. The 5-year EFS and OS were 74.1 ± 5.7% and 86.2 ± 4.5%, respectively. At the end of the follow-up, stage I and II cases have good outcomes with 100% OS. Fourteen patients with testicular tumors, whose histologic types were exclusively YST, have EFS. The survival probability is shown in Fig. 2. The outcomes among different groups based on the clinical and biologic features were shown in Table 2 and 3. No difference in EFS or OS was shown among different AFP groups.

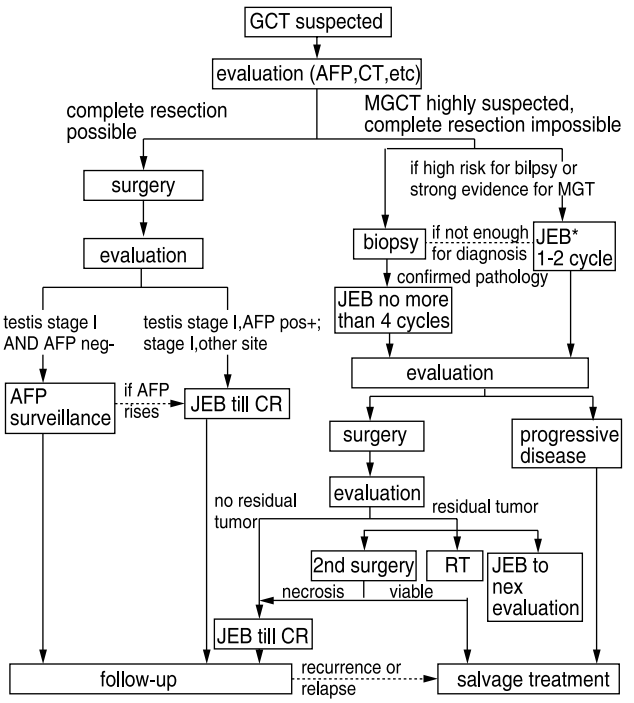

Fig. 2 General treatment schema for pediatric germ cell tumors in our center

Among 58 cases initially diagnosed in our center, 11 were recurrent and refractory. These cases, together with 14 referral cases, were studied in the salvage group. These patients were pretreated with surgery along with JEB or PEb chemotherapy. In this series with 25 patients, 7 patients had poor response, 13 had initial relapse, and 5 had multiple relapses. Among 16 patients who underwent second-look surgery, post-surgical evaluation demonstrated that 8 patients had finally achieved R0, 4 achieved R1, and 4 achieved R2. Further histopathologic examination revealed tumor necrosis in 9 specimens, malignant teratoma in 4, and viable tumor in 3. It should be noted that patients with R0 resection and necrotic tissue after second-look surgery survived. Eighteen patients underwent local irradiation. Preoperative irradiation of 18.0–23.4 Gy in 10–13 fractions was performed in 10 patients. Moreover, these patients received postoperative RT. Chemotherapy was performed in all 25 patients. Eleven received the same JEB regimen as initial treatment, 8 received JEB plus PEI regimens, and six received IN with JEB and PEI regimens. Except for five episodes that are unsuitable for response evaluation, the response rates of chemotherapy were 33.3% (2/6) in the poor response group, 55.5% (5/9) in the multiple relapse group, and 58.3% (7/12) in the initial relapse group. The clinical

Table 1 Characteristics of 58 patients with primary MGCT by tumor site (*n*)

	Testis (14)	Ovary (8)	Retroperitoneal and sacrococcygeal region (30)	Vagina (3)	Thorax (3)	Total
Age at diagnosis (years)						
0–1	0	0	4	1	0	5
1–5	11	1	24	2	0	38
5–12	3	7	2	0	3	15
Stage						
I	9	1	2	0	0	12
II	2	1	3	0	0	6
III	3	4	13	2	2	24
IV	0	2	12	1	1	16
AFP (ng/mL)						
< 10,000	11	4	7	1	2	25
10,000 to < 100,000	3	3	16	2	1	25
≥ 100,000	0	1	7	0	0	8
Histology						
Yolk sac tumor	14	4	24	3	1	46
Malignant teratoma	0	3	6	0	2	11
Others	0	1	0	0	0	1

Table 2 Survival analysis of malignant germ cell tumors based on different factors (*n*)

	No. of patients	5-year EFS (%)	*P* value	5-year OS (%)	*P* value
Sex					
Male	25	88.0 ± 6.5	0.042	96.0 ± 3.9	0.07
Female	33	63.6 ± 8.4		78.8 ± 7.1	
Age (years)					
< 1	7	57.1 ± 18.7	0.433	57.1 ± 18.7	0.033
1–5	36	75.0 ± 7.2		88.9 ± 5.2	
5–12	15	80.0 ± 10.3		93.3 ± 6.4	
Stage					
I	12	91.7 ± 8.0	0.314	100	0.074
II	6	83.3 ± 15.2		100	
III	24	70.8 ± 9.3		87.5 ± 6.8	
IV	16	62.5 ± 12.1		68.8 ± 11.6	
Sites					
Testis	14	100	0.047	100	0.222
Ovary	8	75.0 ± 15.3		87.5 ± 11.7	
Extragonadal	36	63.9 ± 8.0		80.6 ± 6.6	
Histology					
YST	46	78.3 ± 6.1	0.147	87.0 ± 5.0	0.693
Non-YST	12	58.3 ± 14.2		83.3 ± 10.8	
AFP level (ng/mL)					
< 10,000	25	68.0 ± 9.3	0.113	88.0 ± 6.5	0.940
10,000–100,000	27	85.2 ± 6.8		85.2 ± 6.8	
≥ 100,000	6	50.0 ± 20.4		83.3 ± 15.2	
Recurrent and refractory cases (*n* = 25)					

Table 3 Prognostic factors analysis of event-free and overall survival for 25 recurrent and refractory malignant germ cell tumors

Category	No. of patients	3-year EFS (%)	*P* value	3-year OS (%)	*P* value
Local irradiation					
Yes	18	50.0±11.8	0.677	77.4±10.0	0.045
No	7	42.9±18.7		42.9±18.7	
Second-look surgery					
Yes	16	62.5±12.1	0.053	80.8±10.0	0.025
No	9	22.2±13.9		44.4±16.6	

Table 4 Clinical parameters and treatment outcomes of 25 recurrent and refractory cases (*n*)

Patient No.	Months after		Recurrence times or Poor response	Sites of recurrence	Histology at		Post-surgical assessment[a]	AFP[b]	Radiation therapy[c] (Gy)	CT regimens	Reponse of CT[d]	Status[e]	Survical Time (months)
	Diag-nosis	End of previous treatment			Diag-nosis	Last Surgery							
1	8			Local	YST	/	/	↑↑	/	JEB	No	DOD	10
2	4	1	multiple	Local	YST	/	/	↑↑↑	/	JEB,PEI	Yes	PD	
	8	2		Combined		/	/	↑↑	/	JEB,PEI,IN	No	DOD	10
3	2	0	Poor response	Combined	YST	/	/	↑↑	/	JEB	No	DOD	2
4	5	0	Poor response	Local	YST	/	/	↑↑↑	/	JEB	No	DOD	2
5	13	6	1st	Local	YST	necrosis	R0	↑↑	45	JEB	Yes	2° CR	52+
6	8	1	1st	Local	YST	necrosis	R1	↑↑	45	JEB,PEI	Yes	SD	58+
7	3	0	Poor response	Local	MT	MT	R2	↑	18+27	JEB	No	2° CR	34+
8	15	9	1st	Local	MT	necrosis	R0	-	18+27	JEB	Yes	SD	38+
9	14	8	multiple	Local	YST	viable	R0	↑↑↑	23.4+21.6	JEB	No	PR	
	17	0		Local		necrosis	R0	↑↑	/	JEB,PEI,IN	No	PR	50+
10	10	4	multiple	Distant	MT	MT	R1	↑↑	/	JEB,PEI	N/A	PR	
	16	1		Local		/	/	↑	/	JEB,PEI	Yes	PR	
	22	2		Local		MT	R0	↑	/	JEB,PEI	Yes	SD	37+
11	16	7	1st	Local	MT	MT	R0	↑	23.4+27	JEB	No	SD	57+
12	6	2	Poor response	Distant	YST	/	/	↑↑	36	JEB,PEI,IN	Yes	PR	45+
13	4	1	multiple	Local	YST	/	/	↑↑↑	45	JEB	Yes	PR	
	6	0		Distant		/	/	↑↑	/	JEB,PEI	Yes	PD	
	13	1		Combined		/	/	↑↑↑	/	JEB,PEI,IN	No	DOD	15
14	21	13	1st	Local	MT	MT	R1	↑↑	45	JEB	N/A	2°CR	31+
15	9	3	1st	Distant	YST	necrosis	R1	↑↑↑	/	JEB,PEI,IN	No	SD	39+
16	7	2	multiple	Local	YST	necrosis	R1	↑↑	23.4+21.6	JEB,PEI	N/A	2° CR	
	15	3		Combined		necrosis	R0	↑↑	/	JEB,PEI	N/A	3° CR	28+
17	6	1	1st	Local	YST	necrosis	R2	↑↑	18+27	JEB,PEI	Yes	2° CR	42+
18	14	5	1st	Local	MT	viable	R2	↑↑	18+27	JEB	No	DOD	26
19	6	0	Poor response	Combined	MT	viable	R1	↑	18+27	JEB,PEI	No	DOD	18
20	8	2	1st	Local	YST	/	/	↑↑↑	45	JEB,PEI	No	DOD	8
21	9	2	1st	Local	YST	necrosis	R0	↑↑	/	JEB,PEI	Yes	2° CR	38+
22	7	1	1st	Local	YST	/	/	↑	45	JEB	Yes	2° CR	46+
23	10	3	1st	Local	YST	/	/	↑↑	45	JEB	Yes	2° CR	36+
24	6	2	Poor response	Local	YST	necrosis	R2	↑↑↑	18+27	JEB,PEI,IN	Yes	2° CR	24+
25	4	1	Poor response	Local	YST	viable	R0	↑↑	18+27	JEB,PEI	N/A	2° CR	36+

a: R0, tumor totally removed, no residual tumor detectable macroscopically or microscopically; R1, tumor mostly removed, no tumor detectable macroscopically but residual tumor tissue detected microscopically; R2, tumor resection, residual tumor detectable macroscopically.
b: ↑↑, <1,000 ng/mL; ↑↑↑, 1000-<10,000 ng/mL; ↑↑↑↑, >10,000 ng/mL.
c: Local volume of irradiation is shown as preoperative dose + postoperative dose. If not indicated, the entire dose was administered postoperatively.
d: CT, chemotherapy; chemotherapy response was indicated by a decrease in tumor in size in imaging or satisfactory calculated decline in tumor marker.
e: DOD, die of disease; CR, complete remission, the absence of any detectable disease, including normal serum levels of α-fetoprotein; PR, partial remission, the absence of new lesions and at least a 30% decrease in the sum of the longest diameters of target lesions; PD, progressive disease; on the basis of any of the following criteria: a ≥ 20% increase in the sum of the longest diameters of target lesions, new lesions, or disease sites or increases in the serum tumor levels; SD, stable disease, for responses that did not meet the criteria for complete remission, partial remission, or progressive disease.

parameters, treatment responses, and outcomes of these recurrent and refractory cases are shown in Table 4. With a median follow-up duration of 36 months, 17 patients survived, and the 3-year EFS and OS in the patients in this series were 48.0 ± 10.0% and 67.8 ± 9.4%, respectively. In the univariate analysis of prognostic factors, we found a significant difference in OS between patients treated with or without local irradiation (77.4 ± 10.0% vs 42.9 ± 18.7%, P = 0.045) and those treated with or without second-look surgery (80.8 ± 10.0% vs 44.4 ± 16.6%, P = 0.025). All abovementioned factors were included in the multivariate Cox proportional-hazards regression model. The result revealed that no second-look surgery (P = 0.047; 95% confidence interval, 1.02–20.93) could

Table 5 Multivariate analysis with COX regression for recurrent and refractory cases

Factors	Number	HR[a]	95% CI[b]	*P* value
AFP < 10,000 ng/mL	10	2.43	0.45–13.18	0.302
No local irradiation	7	5.65	0.99–32.25	0.051
No second-look surgery	9	5.38	1.15–25.20	0.033

a: HR stands for hazard ratio
b: CI stands for confidence interval

Table 6 Toxicity of salvage chemotherapies

Factors	JEB (*n* = 97)	PEI (*n* = 37)	IN (*n* = 15)
Hematologic toxicity			
Grade 3/4 neutropenia	43	34	6
Grade 3/4 thrombocytopenia	37	34	5
Grade 3/4 infections	9	15	4
Next course delayed > 28 days	16	22	3
Hearing impairment	0	2	0
Renal toxicity			
Acute kidney injury	0	4	0
Hematuria	0	2	0
Tubular dysfunction	0	1	0
Ifosfamide induced neurotoxicity	/	1	/

be considered as individual factor contributing to shorter survival (Table 5).

Among 58 patients with primary tumors, 53 received a total of 278 courses of JEB regimen chemotherapy. The principal toxicities were hematologic abnormalities, mainly neutropenia and thrombocytopenia. A total of 37 courses of PEI and 15 courses of IN were performed in patients with recurrent and refractory tumors. We have observed neither secondary malignancy nor pulmonary fibrosis due to chemotherapy in survivors. Hearing impairment and renal toxicity were rare in patients treated with JEB regimen. One patient developed moderate ifosfamide-induced neurotoxicity and was detoxified with methylene blue. The chemotherapy complications are presented in Table 6.

Discussion

In this study, we enrolled children and adolescents aged < 12 years with extracranial MGCTs. We found that these children had generally good outcomes. The EFS and OS are slightly inferior compared to the COG or United Kingdom study group's result [14]. Among 8 death events in our center, 4 occurred in the first six months after diagnosis. Two patients had just undergone one to two courses of chemotherapy and abandoned the treatment due to financial restraint and eventually died. One 10-month-old boy died due to severe infection after chemotherapy. With the gradual improvement of the medical security system and supportive care in the last few years, the abandonment and treatment-related death rates in GCTs are now extremely low in our center.

Cisplatin-based PEb and carboplatin-based JEB regimens are both first-line chemotherapies for pediatric and adolescent patients with GCTs [6, 15]. Our hospital was one of the first few pediatric cancer centers in China that adopted JEB chemotherapy, and this study has shown the general outcome of childhood MGCTs in the Chinese population aged < 12 years. Due to the age limitation for admission in our center, histologic types, which are more prevalent in adolescents and young adults such as germinoma, embryonal carcinoma, choriocarcinoma, ovarian tumors, and testicular non-YSTs, are rarely observed in this age group. Therefore, the distribution of cases with respect to tumor site or histologic type and outcome of specific subgroups may have some difference from those in existing literature. Patients with stage I testicular tumor showed excellent outcomes and are recommended to undergo a "watch and see" strategy if the AFP level normalizes postoperatively [16]. Four boys in the study had "overtreatment" of postoperative chemotherapy and had EFS. They were not excluded from the analysis.

Although the outcome of pediatric MGCTs with the combined effort of surgical resection and platinum-based chemotherapy is generally optimistic, a challenge still exists on improving the prognosis for recurrent and relapse cases, especially in a pediatric cancer institution with limited medical resources. In our study, recurrent and refractory cases among primary cases were organized and evaluated together with cases referred from other centers.

Increased serum AFP levels usually indicate either residual tumor postoperatively or tumor progression, and tumor relapses of MGCTs are always reflected in the AFP level. In the COG AGCT 0132 study, 23 of 25 patients with stage I ovarian tumors had elevated AFP levels at diagnosis, and all 12 relapse episodes were induced by AFP level elevation [17]. In this study, 54 of 58 patients with primary MGCT had elevated serum AFP levels at diagnosis. Ten of eleven patients with recurrent and refractory tumors had elevated AFP levels during the occurrence of the event. A study on adult GCTs demonstrated that the rate of AFP level decline during chemotherapy has prognostic value independent of risk [18]. Therefore, AFP was considered to be an ideal marker for tumor surveillance and response evaluation in chemotherapy.

Many children with recurrent GCTs will have local relapse rather than disseminated relapse in adults; therefore, multimodality efforts with the aim of achieving good local control are considered the mainstay of the salvage approach. In the German MAKEI study, the 5-year EFS and OS in all 22 patients with relapse MGCT

reached 0.3 ± 0.1 and 0.42 ± 0.11, respectively, with salvage therapy and indicated that complete resection of the local lesion was critical in salvage treatment. For most relapse or refractory tumors, resection might be impossible when tumors have infiltrated adjacent nerves and bones because radical surgery can be mutilating. Preoperative platinum-based chemotherapy, combined with local regional thermochemotherapy, might facilitate complete tumor resection. Local irradiation with doses > 45 Gy contributed to a favorable outcome in patients with residual tumor [19]. In the later MAKEI phase 2 study on regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular MGCTs, a multimodal strategy integrating PEI-regional deep hyperthermia and surgical resection with or without radiation had successfully promoted the long-term outcome of these patients with treatment almost similar to those undergoing first-line treatment [20]. However, regional deep hyperthermia is resource consuming and not accessible in many children's cancer centers. Besides postoperative RT, preoperative RT could be considered in childhood unresectable tumors to facilitate surgical resection. In studies on adult patients with rectal cancer, a relative improvement of 24% in disease-free survival was recorded in patients undergoing preoperative RT [21]. Preoperative RT had shown its value in local control in pediatric and young adult patients with unresectable nonrhabdomyosarcoma soft-tissue sarcoma [22]. We have observed some effects on the tumor shrinkage and inhibition of vascularization of preoperative irradiation in previous clinical practice. In this study, patients undergoing preoperative RT had achieved satisfactory outcomes (5/10 had complete remission, 1/10 had partial remission, 2/10 had stable disease, and 2/10 died of the disease) comparable to those in MAKEI PEI-regional deep hyperthermia salvage therapy.

The major goal of chemotherapy for relapse MGCTs should be bridging to complete tumor resection. The regimen administered before relapse or progression is an important concern. It seems that patients with recurrent sacrococcygeal MGCTs who were treated with less-intensive regimens (such as insufficient dose of etoposide and carboplatin) can be successfully treated with intensive chemotherapy [23–24]. However, treatment of patients with an intensive pretreatment may be problematic [18]. Studies on adults receiving GOP (gemcitabine, oxaliplatin, paclitaxel), TIP (paclitaxel, ifosfamide, cisplatin) and IN regimens for relapse GCTs indicated that platinum-based second-line chemotherapy might be utilized for recurrent and refractory childhood MGCTs to facilitate local control [12, 25–26]. The initial chemotherapy in this cohort was mainly the JEB regimen. At the time of recurrence, JEB, PEI, and IN regimens had been administered to these patients. The single relapse group had higher response rate to chemotherapy than the other two groups. Nishikawa et al. reported that IN regimen led to normalization of serum tumor marker levels in 45% of patients with relapse tumors who underwent surgical resection [12]. Six patients (Nos. 2, 6, 10, 13, 17, 21) achieved response after PEI regimen, and 2 patients (Nos. 12, 14) showed responses to IN regimen after failure of JEB and PEI regimens. The efficacy of these salvage regimens needs to be further verified through a uniform study design. Patients with recurrent or refractory tumors treated with or without RT and second-look surgery have revealed a significant difference in survival rate. After including the AFP group, staging, and these factors in the multivariate Cox regression model, the multivariate analysis demonstrated that no surgery could be considered as individual factor contributing to poorer prognosis. This result has confirmed the viewpoint that a complete resection of local recurrent tumor represents the cornerstone of salvage treatment [27]. We attribute this salvage rate in our center to the successful implementation of preoperative and postoperative local irradiation, second-line chemotherapy, careful surgery, and sincere cooperation of the multidisciplinary team in the children's cancer center. There were no treatment-related death, secondary malignancy, or lung fibrosis and few nephrotoxicities, ototoxicities, and neurotoxicities in the chemotherapy group in the median follow-up duration of 36 months. However, local irradiation in pediatric patients at the gonadal and extragonadal sites may cause a series of short-term and long-term side effects. Further follow-up is needed to observe the subacute and late visceral effects among survivors [28–29].

Conclusion

The treatment result from our center for childhood extracranial MGCTs is generally optimistic. For recurrent and refractory cases, the treatment approaches for local control including pre- and postoperative RT, salvage chemotherapy such as PEI and IN regimens, and second-look surgery were successfully performed, and satisfactory outcomes were achieved without major morbidity.

Acknowledgments

We greatly appreciate the pediatric cancer multidisciplinary team from our center (including pediatric oncologists, surgeons, radiation therapists, radiologists, pathologists, specialty nurses, and social workers) for their collaborative work to the treatment plan and dedication to the care of our patients and their families.

Conflicts of interest

The authors indicate no potential conflicts of interest.

References

1. Ward E, DeSantis C, Robbins A, *et al*. Childhood and Adolescent Cancer Statistics, 2014. CA Cancer J Clin, 2014, 64: 83–103.
2. Schneider DT, Schuster AE, Fritsch MK, *et al*. Multipoint imprinting analysis indicates a common precursor cell for gonadal and nongonadal pediatric germ cell tumors. Cancer Res, 2001, 61: 7268–7276.
3. Schneider DT, Calaminus G, Koch S, *et al*. Epidemiologic analysis of 1,442 children and adolescents registered in the German germ cell tumor protocols. Pediatr Blood Cancer, 2004, 42: 169–175.
4. Mann JR, Pearson D, Barrett A, *et al*. Results of the United Kingdom Children's Cancer Study Group's malignant germ cell tumor studies. Cancer. 1989, 63: 1657–1667.
5. Mann JR, Raafat F, Robinson K, *et al*. The United Kingdom Children's Cancer Study Group's second germ cell tumor study: carboplatin, etoposide, and bleomycin are effective treatment for children with malignant extracranial germ cell tumors, with acceptable toxicity. J Clin Oncol, 2000, 18: 3809–3818.
6. Cushing B, Giller R, Cullen JW, *et al*. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study-Pediatric Oncology Group 9049 and Children's Cancer Group 8882. J Clin Oncol, 2004, 22: 2691–2700.
7. Wessalowski R, Kruck H, Pape H, *et al*. Hyperthermia for the treatment of patients with malignant germ cell tumors: a phase I/II study in ten children and adolescents with recurrent or refractory tumors. Cancer, 1998, 82: 793–800.
8. Blohm ME, Vesterling-Horner D, Calaminus G, *et al*. Alpha 1-fetoprotein (AFP) reference values in infants up to 2 yeas of age. Pediatr Hematol Oncol, 1998, 15: 135–142.
9. Rogers PC, Olson TA, Cullen JW, *et al*. Treatment of children and adolescents with stage II testicular and stages I and II ovarian malignant germ cell tumors: A Pediatric Intergroup Study-Pediatric Oncology Group 9048 and Children's Cancer Group 8891. J Clin Oncol, 2004, 22: 3563–3569.
10. Marina NM, Rodman J, Shema SJ, *et al*. Phase I study of escalated targeted doses of carboplatin combined with ifosfamide and etoposide in children with relapsed solid tumors. J Clin Oncol,1993,11: 554.
11. Farhat F, Culine S, Théodore C, *et al*. Cisplatin and ifosfamide with either vinblastine or etoposide as salvage therapy for refractory or relapsing germ cell tumor patients: the Institut Gustave Roussy experience. Cancer, 1996, 77: 1193–1197.
12. Nishikawa M, Miyake H, Fujisawa M. Irinotecan and nedaplatin as salvage therapy for patients with advanced germ cell tumors following intensive treatment with cisplatin-based combination chemotherapies. Int J Clin Oncol, 2016, 21: 162–167.
13. Bagatell R, London WB, Wagner LM, *et al*. Phase II study of irinotecan and temozolomide in children with relapsed or refractory neuroblastoma: a Children's Oncology Group study. J Clin Oncol, 2011, 29: 208–213.
14. Frazier AL, Hale JP, Rodriguez-Galindo C, *et al*. Revised risk classification for pediatric extracranial germ cell tumors based on 25 years of clinical trial data from the United Kingdom and United States. J Clin Oncol, 2015, 33: 195–201.
15. Williams SD, Birch R, Einhorn LH, *et al*. Treatment of disseminated germ-cell tumors with cisplatin, bleomycin, and either vinblastine or etoposide. N Engl J Med,1987, 316: 1435–1440.
16. Schlatter M, Rescorla F, Giller R, *et al*. Excellent outcome in patients with stage I germ cell tumors of the testes: a study of the Children's Cancer Group/Pediatric Oncology Group. J Pediatr Surg, 2003, 38: 319–324.
17. DF Billmire, JW Cullen, FJ Rescorla. *et al*. Surveillance after initial surgery for pediatric and adolescent girls with stage I ovarian germ cell tumors: report from the Children's Oncology Group. J Clin Oncol, 2014, 32: 465–470.
18. Mazumdar M, Bajorin DF, Bacik J, *et al*. Predicting outcome to chemotherapy in patients with germ cell tumors: the value of the rate of decline of human chorionic gonadotrophin and alpha-fetoprotein during therapy. J Clin Oncol, 2001,19: 2534–2541.
19. Schneider DT, Wessalowski R, Calaminus G, *et al*. Treatment of recurrent malignant sacrococcygeal germ cell tumors: analysis of 22 patients registered in the German protocols MAKEI 83/86, 89, and 96. J Clin Oncol, 2001,19: 1951–1960.
20. Wessalowski R, Schneider DT, Mils O, *et al*. Regional deep hyperthermia for salvage treatment of children and adolescents with refractory or recurrent non-testicular malignant germ-cell tumours: an open-label, non-randomised, single-institution, phase 2 study. Lancet Oncol, 2013,14: 843–852.
21. Sebag-Montefiore D, Stephens RJ, Steele R, *et al*. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet, 2009, 373: 811–820.
22. Smith KB, Indelicato DJ, Knapik JA, *et al*. Definitive radiotherapy for unresectable pediatric and young adult nonrhabdomyosarcoma soft tissue sarcoma. Pediatr Blood Cancer, 2011, 57: 247–251.
23. Baranzelli MC, Kramar A, Bouffet E, *et al*. Prognostic factors in children with localized malignant nonseminomatous germ cell tumors. J Clin Oncol,1999, 17: 1212–1218.
24. Schneider DT, Calaminus G, Reinhard H, *et al*. Primary mediastinal germ cell tumors in children and adolescents: results of the German cooperative protocols MAKEI 83/86, 89, and 96. J Clin Oncol, 2000, 18: 832–839.
25. Bokemeyer C, Oechsle K, Honecker F, *et al*. Combination chemotherapy with gemcitabine, oxaliplatin, and paclitaxel in patients with cisplatin-refractory or multiply relapsed germ-cell tumors: a study of the German Testicular Cancer Study Group. Ann Oncol, 2008,19: 448–453.
26. Kondagunta GV, Bacik J, Donadio A, *et al*. Combination of paclitaxel, ifosfamide, and cisplatin is an effective second-line therapy for patients with relapsed testicular germ cell tumors. J Clin Oncol, 2005, 23: 6549–6555.
27. Göbel U, Schneider DT, Calaminus G, *et al*. Multimodal treatment of malignant sacrococcygeal germ cell tumors: A prospective analysis of 66 patients of the German cooperative protocols MAKEI 83/86 and 89. J Clin Oncol, 2001,19: 1943–1950.
28. Kenney LB, Cohen LE, Shnorhavorian M, *et al*. Male reproductive health after childhood, adolescent, and young adult cancers: a report from the Children's Oncology Group. J Clin Oncol, 2012, 30: 3408–3416.
29. Wo JY, Viswanathan AN. Impact of radiotherapy on fertility, pregnancy, and neonatal outcomes in female cancer patients. Int J Radiat Oncol Biol Phys, 2009, 73: 1304–1312.

DOI 10.1007/s10330-019-0362-2
Cite this article as: He KJ, Yuan XJ, Tan Z. Treatment results of childhood extracranial malignant germ cell tumors and the salvage approach for recurrent and refractory cases: a single-center report. Oncol Transl Med, 2019, 5: 229–236.